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(71) Applicant (*for all designated States except US*): **ANTICANCER, INC.** [US/US]; 7917 Ostrow Street, San Diego, CA 92111-3604 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **BARANOV, Eugene** [AU/US]; 8324 Regents Road #1-F, San Diego, CA 92122 (US). **YANG, Meng** [CN/US]; 6699 Beadnell Way #207, San Diego, CA 92117 (US).

(74) Agents: **MULLEN, James, J., III** et al.; Morrison & Foerster LLP, 3811 Valley Centre Drive, Suite 500, San Diego, CA 92130-2332 (US).

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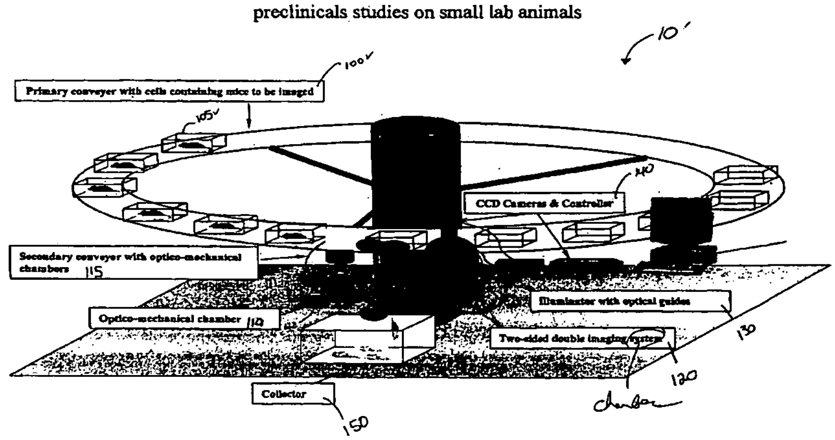
(54) Title: MODULAR SYSTEM FOR MULTI-COLOR, WHOLE BODY FLUORESCENCE IMAGING

Functional scheme of high-throughput fluorescence based non-invasive imaging system for preclinicals studies on small lab animals



(57) Abstract: The disclosed invention relates to a modular system (10) for multi-color, whole-body fluorescence imaging, comprising a primary conveyor (100) comprising a holding cell (105) for holding a subject; and optico-mechanical chamber (110) comprising an entry port (111) and an exit port (112), wherein the entry port is adapted to receive the subject from the holding cell; a secondary conveyor (115) comprising the optico-mechanical chamber; a two-sided double imaging chamber (120) adapted to receive the optico-mechanical chamber provided by the secondary conveyor; an illuminator (130) comprising a plurality of optical guides (131), wherein the optical guides illuminate the two-sided double imaging chamber; and an imaging system (140) comprising a camera (141) and a controller (142), wherein the camera is positioned to image the subject within the optico-mechanical chamber within the two-sided double imaging chamber and the controller can access images of the gathered by the camera.

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MODULAR SYSTEM FOR MULTI-COLOR, WHOLE BODY FLUORESCENCE IMAGING

FIELD OF THE INVENTION

[0001] The disclosed invention relates to a system of imaging subjects that is non-invasive, provides whole body images, and is adapted to handle a plurality of subjects.

BACKGROUND OF THE INVENTION

[0002] Animal models of human cancer have undergone profound improvements. It is now possible to examine tumor growth and metastasis using fluorescence emitting tumor cells. Recent developments in the field have provided reagents that permit non-invasive whole body imaging of subjects. The disclosed invention provides a system of imaging a plurality of subjects using multi-color fluorescence probes.

BRIEF SUMMARY OF THE INVENTION

[0003] The disclosed invention relates to a modular system (10) for multi-color, whole-body fluorescence imaging, comprising a primary conveyor (100) comprising a holding cell (105) for holding a subject; an optico-mechanical chamber (110) comprising an entry port (111) and an exit port (112), wherein the entry port is adapted to receive the subject from the holding cell; a secondary conveyor (115) comprising the optico-mechanical chamber; a two-sided double imaging chamber (120) adapted to receive the optico-mechanical chamber provided by the secondary conveyor; an illuminator (130) comprising a plurality of optical guides (131), wherein the optical guides illuminate the two-sided double imaging chamber; and an imaging system (140) comprising a camera (141) and a controller (142), wherein the camera is positioned to image the subject within the optico-mechanical chamber within the two-sided double imaging chamber and the controller can access images of the gathered by the camera.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] FIG. 1 is a schematic view of a high-throughput non-invasive fluorescence imaging system.

[0005] FIG. 2 is a cross-section schematic view of two-sided double imaging chamber.

DETAILED DESCRIPTION OF THE INVENTION

[0006] The invention described relates to a modular system for multi-color, whole-body fluorescent imaging of subjects. The system contains a transparent imaging changer within which a subject is placed. Cameras include charge-coupled devices (CCD) sufficient for both macro-imaging and micro-imaging. Lighting systems are described that give uniform light throughout the imaging chamber. A conveyor system is also described that is used to deliver subjects to the imaging chamber. Light sources sufficiently powerful for all types of macro- and micro-imaging of fluorescence in vivo with resolution at the subcellular level at various depths in the subject's body are described. Software is used to distinguish the fluorescence signal above the background and quantify the signal with regard to area and intensity. The system is particularly applicable for imaging of animal subjects that have cells and tissues that express fluorescent proteins introduced transgenically.

[0007] The described invention relates to a non-invasive system for imaging subjects emitting a fluorescent signal. A preferred embodiment of the system (10) is shown in FIGURE 1. The system comprises a primary conveyer system (100) that provides the plurality of subjects to the imaging components of the system. The primary conveyer shown in the figure comprises a plurality of subject cells (105), which house each subject to be imaged. An individual subject cell (105) will typically be an enclosed structure having a port adjacent to the conveyer that is of sufficient diameter to permit the passage of the subject out of the subject cell. As illustrated, the primary conveyer is circular and revolves around a central drive. Alternatively embodiments of conveyers are also contemplated. For example, the conveyer may be a belt, such as a linear belt.

[0008] The system further comprises a secondary conveyer (115) comprising a one or more optico-mechanical chambers (110). The optico-mechanical chambers comprise an entry port (111) and an exit port (112) which may be moved to enclose the optico-mechanical chamber. As illustrated, the secondary conveyer comprises a plurality of optico-mechanical chambers that are rotated under the primary conveyer and the subject cells positioned on the primary conveyer.

[0009] As passes the optico-mechanical chamber passes under the primary conveyer system, the entry port of the optico-mechanical chamber opens. The port in the subject cell on the primary conveyer directly over the optico-mechanical chamber opens to permit

the subject to pass from the subject cell to the optico-mechanical chamber. After the subject is passed into the optico-mechanical chamber, the secondary conveyer passes the optico-mechanical chamber with the subject to the next station and closing the entry port (111) to contain the subject within the chamber.

[0010] As illustrated in FIGURE 1, an optico-mechanical chamber (110) containing a subject is passed into a two-sided double imaging chamber (120). The imaging chamber is connected to an illuminator (130) by a plurality of optical guides (131).

[0011] To visualize fluorescent probes of different wavelengths simultaneously, such as the green fluorescent protein (GFP) or red fluorescent protein (RFP) excitation is produced through a filter, such as a D425/60 band pass filter and a 370 DCXR dichroic mirror. These devices are preferably associated with the optical guides (131).

[0012] The imaging chamber is also connected to at least one imaging device (140), such as a camera, which is in turn connected to a controller. The imaging device and controller collect signals from the subject in the two-sided double imaging system and pass those signals to an analysis device (150) that processes the imaging data.

[0013] FIGURE 2 shows a cross-section of a two-sided double imaging chamber (120). The imaging chamber (120) serves as a light box for gathering fluorescence data from a subject. The imaging chamber typically comprises an external dome (210) comprising an outer surface (211) and an inner surface (212). The external dome is constructed of opaque materials do not permit light to pass into the interior portion of the imaging chamber. In a preferred embodiment, the outer surface of the external dome has a mirrored surface.

[0014] Disposed within the external dome (210) is a scattering dome (220). Through both the external and scattering domes are disposed a plurality of a plurality of optical guide adaptors (205) and camera adaptors (230). The optical guide adaptors that permit an optical guide (131) to be inserted therein and pass electromagnetic energy into the scattering dome.

[0015] The scattering dome (220) positioned adjacent to the inner surface of the external dome distributes the electromagnetic energy provided by the optical guides such that uniform excitation electromagnetic energy to the body of the subject.

[0016] An emission filter (200) is shown in the figure as being positioned adjacent to the first camera adaptor and the scattering dome. Preferably the emission filter is tunable. Additionally, it is preferable that the filter is of sufficient narrow band to distinguish

between closely-related emission spectra. An example of an emission filter is the long pass filter GG475 (CHROMA TECHNOLOGY, Brattleboro, VT).

[0017] The optical guides provide excitation stimulus to the subject such that a fluorescent probe or protein present in the subject will fluoresce in response to the stimulus supplied. In a preferred embodiment, the optical guides provided laser light at a given wavelength to the internal portion of the imaging chamber and the scattering dome. In an alternately preferred embodiment, the optical guides provide dual-photon delivery to the scattering dome.

[0018] As shown in FIGURE 2, a first camera (140a) is disposed in a first camera adaptor (230a) and a second camera is disposed in a second camera adaptor (230b) such that the cameras are positioned to receive electromagnetic energy emitted from the subject in response to the excitation signal provided by the optical guides.

[0019] Preferably a camera used with the system is sufficiently sensitive to image fluorescence produced by any organ in the subject. More preferably, the camera can image a single fluorescent cell in the subject. A preferred camera is a C5810 3-chip Cool-Color charge-coupled device camera (HAMAMATSU PHOTONICS, Hamamatsu City, Japan). Additional optics can be provided to the camera used with the disclosed device to provide greater image resolution. For example, a Leica MZ12 fluorescence microscope may be coupled to the Hamamatsu C5810 camera to provide better image resolution.

[0020] Images colleted by the cameras are processed for contrast and brightness and analyzed typically using a personal computer. For example, in a preferred embodiment, images are analyzed using IMAE PRO PLUS v.4.0 software (MEDIA CYBERNETICS, Silver Spring, MD). High resolution images of 1024 x 724 pixels are preferably captured directly on an IBM PC or continuously through video output.

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CLAIMS

What is claimed is:

1. A modular system (10) for multi-color, whole-body fluorescence imaging, comprising:

a primary conveyor (100) comprising a holding cell (105) for holding a subject;

an optico-mechanical chamber (110) comprising an entry port (111) and an exit port (112), wherein the entry port is adapted to receive the subject from the holding cell;

a secondary conveyor (115) comprising the optico-mechanical chamber;

a two-sided double imaging chamber (120) adapted to receive the optico-mechanical chamber provided by the secondary conveyor;

an illuminator (130) comprising a plurality of optical guides (131), wherein the optical guides illuminate the two-sided double imaging chamber;

an imaging system (140) comprising a camera (141) and a controller (142), wherein the camera is positioned to image the subject within the optico-mechanical chamber within the two-sided double imaging chamber and the controller can access images of the gathered by the camera.

2. The system of claim 1, further comprising an image analysis device for storing and analyzing images produced by the cameras of the system.

3. The system of claim 2, wherein the image analysis device uses software that automatically models any area emitting fluorescence from the subject.

4. The system of claim 3, wherein the software calculates the size of the modeled area.

5. The system of claim 3, wherein the software calculates the intensity of signal emitted from the modeled area.

6. The system of clam 1, wherein the camera is sufficiently sensitive to image fluorescence emitted from the subject.

7. The system of claim 6, wherein the camera is sufficiently sensitive to image fluorescence emitted from a single cell in the subject.

8. A two-sided double imaging chamber (120) comprising:

an external dome (210) comprising an outer surface (211) and an inner surface (212);

a scattering dome (220) positioned adjacent to the inner surface;

a plurality of optical guide adaptors (205) in the external dome that permit an optical guide (131) to be inserted therein and pass electromagnetic energy into the scattering dome;

a first camera adaptor (230a) and a second camera adaptor (230b) in the external dome that permit a first camera (140a) and a second camera (140b) to be inserted therein and receive electromagnetic energy; and

an emission filter (200) position adjacent to the first camera adaptor and the scattering dome;

9. The chamber of claim 8, wherein the external dome further comprises a mirrored external surface.

10. The chamber of claim 8, wherein the optical guide provides laser light at a given wavelength.

11. The chamber of claim 10, wherein the optical guide provides dual-photon delivery to the scattering dome.

12. The chamber of claim 8, wherein the emission filter is tunable.

13. The chamber of claim 8, wherein the filter is of sufficient narrow band to distinguish between closely-related emission spectra.

14. The chamber of claim 8, wherein the scattering dome provides uniform lighting from the optical guides.

15. The chamber of claim 8, wherein the camera are sufficiently sensitive to image fluorescence produced by any organ in the subject.

16. The chamber of claim 15, wherein the camera can image a single fluorescent cell in the subject.

17. The chamber of claim 5, wherein the scattering dome scatters light uniformly such that the entire subject may be imaged.

FIGURE 1

Functional scheme of high-throughput fluorescence based non-invasive imaging system for preclinicals studies on small lab animals

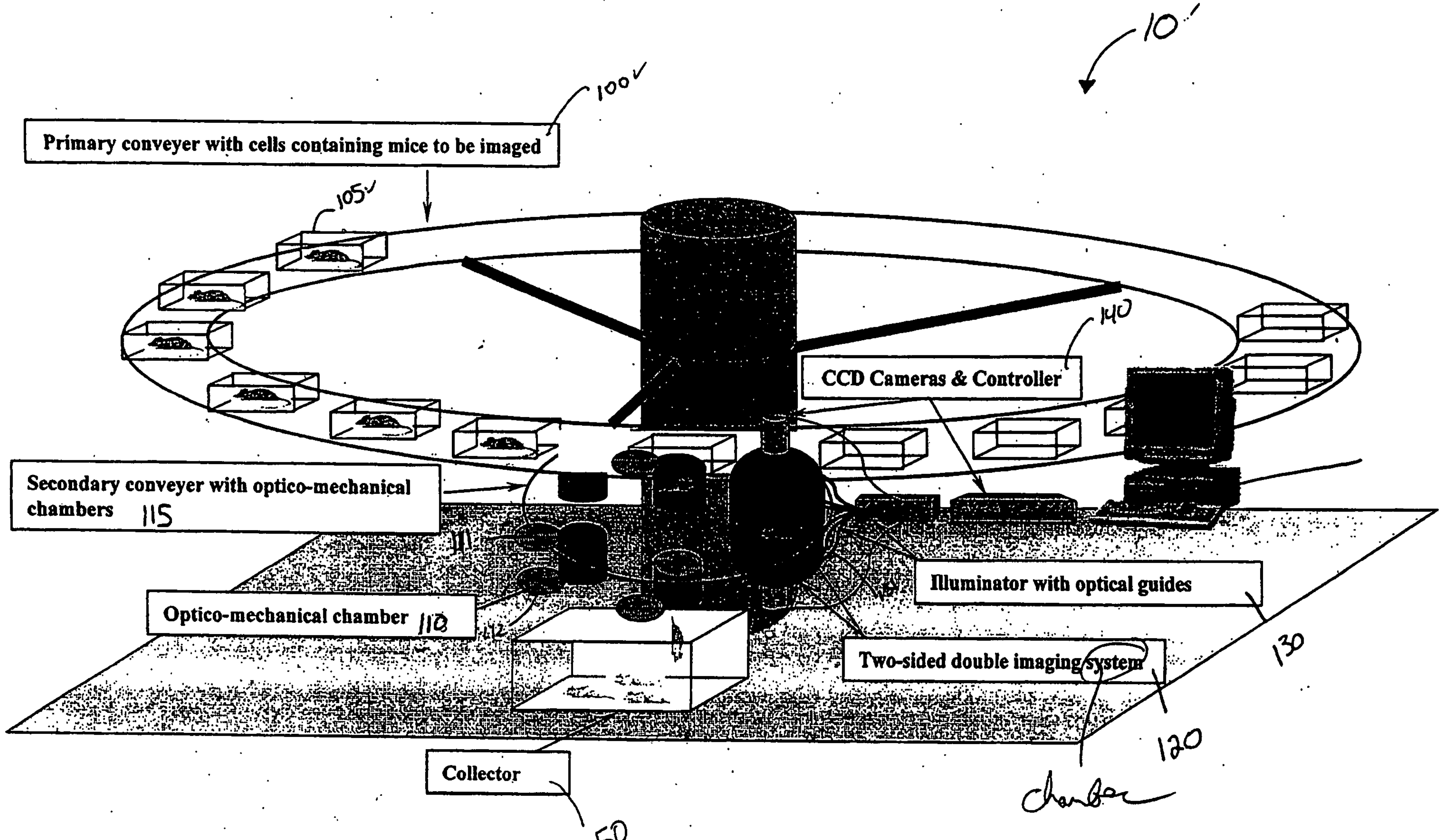

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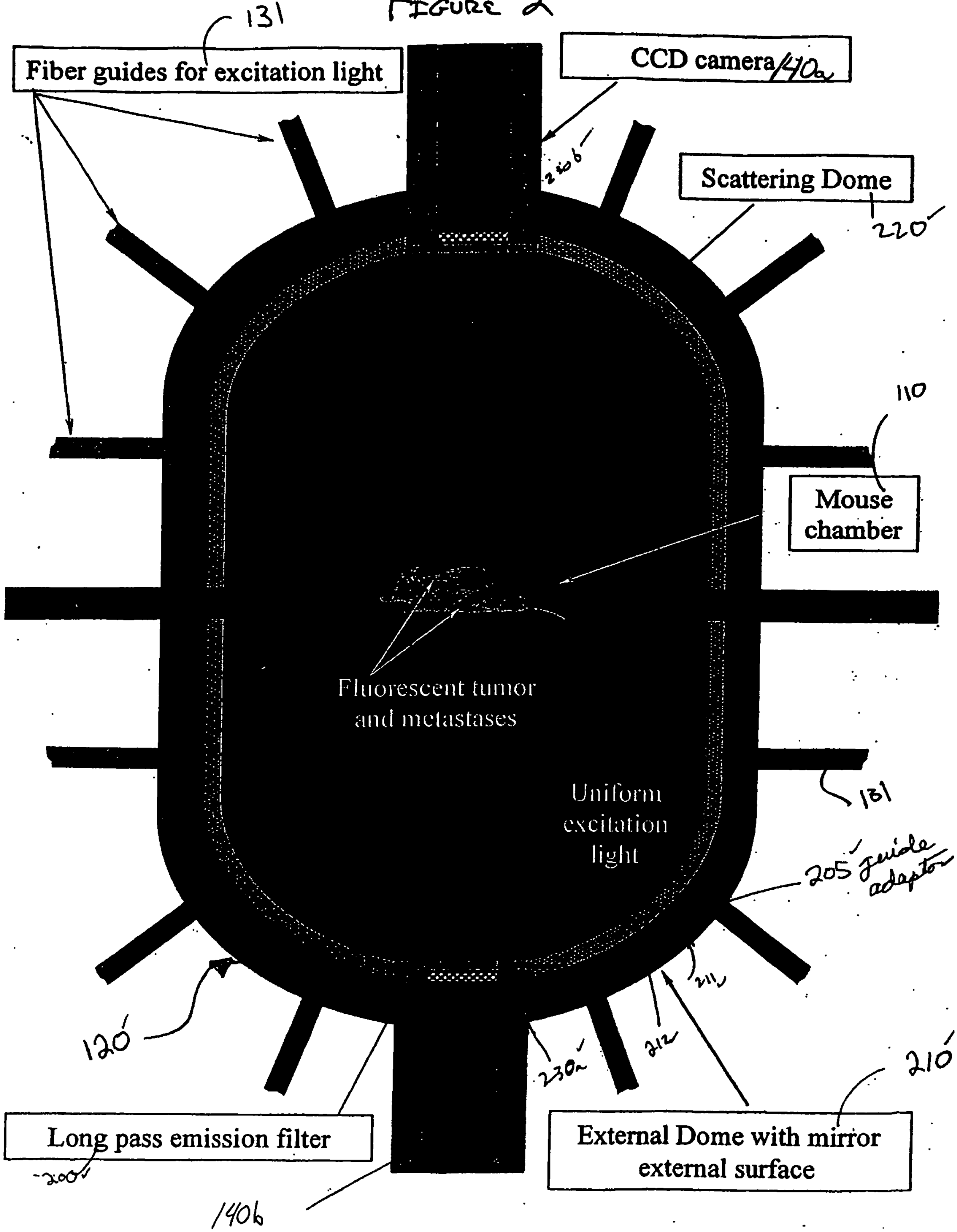
FIGURE 2



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